SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Morfin Kalceks, 10 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Morphine hydrochloride 10 mg/ml equivalent to morphine 7.6 mg/ml.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear, colourless or yellowish liquid, pH 3-5.
Osmolarity 0.035-0.055 Osmol/L.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Severe pain conditions which can be adequately managed only with opioid analgesics.

4.2 Posology and method of administration
Posology
Administration and posology should be adjusted according to the nature and severity of the pain as well as the general condition of the patient. Individual criteria for the dose are dependent on the patient’s age, weight, pain severity and medical and analgesic history.

Adults: 1-1.5 ml solution for injection (10-15 mg morphine hydrochloride) subcutaneously or intramuscularly 1-3 times daily. In urgent cases morphine can be administered slowly intravenously.

Elderly
Caution should be exercised and the dose initially reduced in morphine treatment.

Hepatic and renal impairment
Caution should be exercised and the dose initially reduced in morphine treatment.

The dose may need reduction in patients with bronchial asthma, upper respiratory tract obstruction, skull injuries, peritoneal dialysis, hypotension associated with hypovolemia, hypothyroidism, inflammatory bowel diseases, pancreatitis, biliary passage or ureter spasms.

Treatment monitoring
Nausea, vomiting and obstipation can sometimes be counteracted by 0.25-0.5 mg atropine subcutaneously. Respiratory depression can be reversed with naloxone.

Discontinuation of therapy
An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore the dose should be gradually reduced prior to discontinuation.
Method of administration
For intravenous, intramuscular or subcutaneous use.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- secretion stagnation in the respiratory tract,
- respiratory depression,
- acute liver disease,
- anxiety conditions during affect by alcohol or hypnotic medicines.

4.4 Special warnings and precautions for use
Caution should be exercised in patients with prostate hypertrophy, myasthenia gravis.
Morphine should not be used in idiopathic pain or in pain with psychopathological characteristics (related to the lack of pain relief).
Morphine alone should not be administered during biliary or renal colic attacks as it may increase the cramp. In these cases morphine should be given in combination with a spasmolytic.
Following encephalitis, the effects of morphine can be enhanced.
Treatment with MAO inhibitors, see section 4.5.

Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

Morphine has an abuse potential similar to other strong agonist opioids, and should be used with particular caution in patients with a history of alcohol or drug abuse.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Dependence and withdrawal (abstinence) syndrome
Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. The risk increases with the time the drug is used, and with higher doses.
Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)
Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Adrenal insufficiency
Opoid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased sex hormones and increased prolactin
Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Morfin Kalceks and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Morfin Kalceks concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Combinations that should be avoided

**Barbiturates**
Barbiturates enhance the respiratory depressive effect of opiates and opioids. The combination should therefore be avoided.

**Small amounts of alcohol**
Small amounts of alcohol can largely increase the weak respiratory depressive effect of morphine. The combination should therefore be avoided.

**MAO inhibitors**
MAO inhibitors can potentiate the effects of morphine (respiratory depression and hypotension). Serotonin syndrome has been reported during concomitant treatment with pethidine and MAO inhibitors, and the emergence of the same reaction cannot be ruled out during concomitant treatment with morphine and MAO inhibitors.

Combinations that may require dose adjustment

**Gabapentin**
Attention should be paid to the risk of CNS symptoms in the choice of treatment. If the two products are given concomitantly, consider reducing the gabapentin dose. Patients should therefore be monitored carefully regarding signs of CNS depression such as somnolence, and the gabapentin or morphine dose should be reduced accordingly.

**Rifampicin**
Rifampicin decreases the plasma concentration of oral morphine strongly enough that higher doses than normal are required for analgesic effect.

**Amitriptyline, clomipramine and nortriptyline**
Amitriptyline, clomipramine and nortriptyline enhance the analgesic effect of morphine, probably caused by increased bioavailability. Dose adjustment may be necessary.

**Combined morphine agonists/antagonists**
Combined morphine agonists/antagonists (*buprenorphine, nalbuphine, pentazocine*) decrease the analgesic effect through competitive inhibition of receptors, which increase the risk of withdrawal symptoms.

Combinations with unclear clinical relevance

**Baclofen**
The combination of morphine and intrathecal administration of Lioresal caused decreased blood pressure in one patient. The risk for this combination to cause apnoea or other CNS symptoms cannot be excluded.

**Hydroxyzine**
Concomitant administration of hydroxyzine and morphine can via additive effect cause increased CNS depression and drowsiness. Switching to a non-sedative antihistamine should be considered.

**Methylphenidate**
Methylphenidate can increase the analgesic effect of morphine. During concomitant administration a reduction of the morphine dose should be considered.

**Nimodipine**
Nimodipine can increase the analgesic effect of morphine. During concomitant administration a reduction of the morphine dose should be considered.

**Ritonavir**
Morphine levels can decrease due to induction of glucuronidation by concomitantly administered ritonavir dosed as an antiretroviral medicinal product or pharmacokinetic booster of other protease inhibitors.

**Sedative medicines such as benzodiazepines or related drugs**
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

### 4.6 Fertility, pregnancy and lactation

**Men and women of childbearing potential**
Due to the mutagenic properties of morphine, it should not be administered to men and women of child-producing/child bearing potential unless effective contraception is assured (see section 5.3).

**Pregnancy**
There are limited amount of data from the use of morphine in pregnant women. Morphine crosses the placenta. Studies in animals have shown reproductive toxicity (see section 5.3). For this reason, morphine must only be used during pregnancy in cases where the maternal benefit clearly outweighs the risk for the child.

Long term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Morphine can prolong or shorten the duration of labour. Morphine can produce respiratory depression in the neonate, if it is administered during labour. New-borns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care. Especially during the 2 to 3 hours before expected partum Morfin Kalceks should only be administered on strict indication and following a mother benefit versus baby risk analysis.

**Breast-feeding**
Morphine is excreted into breast milk, where it reaches higher concentrations than in maternal plasma. Since clinically relevant concentrations of morphine may be reached in nursing infant, breast-feeding is not recommended (see section 5.2).

**Fertility**
There are no clinical data on the effects of morphine on male or female fertility. Animal studies have shown that morphine may reduce fertility (see 5.3 Preclinical safety data).

### 4.7 Effects on ability to drive and use machines

Morfin Kalceks has major influence on the ability to drive and use machines.

### 4.8 Undesirable effects

Approximately 20 % of the patients suffer from nausea and vomiting. Most undesirable effects are dose dependent.
The adverse reactions are presented below in accordance with the MedDRA system organ classification. The frequencies have been assessed in accordance with the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

**Immune system disorders:**
*Not known:* anaphylactoid reactions.

**Endocrine disorders:**
*Common:* increased ADH release.

**Psychiatric disorders:**
*Uncommon:* dysphoria.
*Not known:* euphoria, sleep, memory and concentration disturbances, dependence.

**Nervous system disorders:**
*Common:* sedation, dizziness.
*Uncommon:* respiratory depression, disorientation.
*Not known:* allodynia, hyperalgesia (see section 4.4), hyperhidrosis, convulsions, myoclonus.

**Eye disorders:**
*Common:* miosis.

**Cardiac disorders:**
*Rare:* palpitations, tachycardia, syncope.

**Vascular disorders:**
*Rare:* orthostatic hypotension, hypertension, hypotension, peripheral oedema.

**Respiratory, thoracic and mediastinal disorders:**
*Uncommon:* bronchoconstriction.

**Gastrointestinal disorders:**
*Common:* obstipation, nausea, vomiting.
*Not known:* dry mouth.

**Hepatobiliary disorders:**
*Uncommon:* biliary tract spasm.

**Skin and subcutaneous tissue disorders:**
*Uncommon:* pruritus.
*Not known:* urticaria.

**Renal and urinary disorders:**
*Common:* urinary retention.
*Uncommon:* urinary tract spasm.

**General disorders and administration site conditions:**
*Uncommon:* light-headedness.
*Not known:* drug withdrawal (abstinence) syndrome.

Sedation normally decreases after a few days of administration. Nausea and vomiting usually decrease in long term treatment. Spasms in biliary or urinary tract can occur in predisposed persons. The respiratory depressive effect is dose dependent and is rarely a clinical problem. Dependence and tolerance do normally not cause problems in treatment of severe cancer pain.
Drug dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered, or can sometimes be experienced between doses. For management, see 4.4.

Physiological withdrawal symptoms include: body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, “drug craving” is often involved.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose

Signs of overdose are pin-point pupils, respiratory depression and low blood pressure, pneumonia aspiration. Circulatory disturbances and coma may occur in serious cases. Death may occur from respiratory failure.

Treatment of overdose

If justified, gastric lavage, charcoal, laxative when orally administered. Respiratory depression caused by morphine intoxication can be reversed with naloxone, initially 0.4 mg for adults (children 0.01 mg/kg) slowly intravenously, the dose is gradually increased if necessary. Continuous infusion of naloxone can sometimes be a useful alternative. Respirator treatment on when indicated (with PEEP in pulmonary edema). Naloxone cannot replace respirator treatment in serious intoxication. Intravenous fluid (electrolyte solution, glucose), blood gas control, acidosis correction. Symptomatic therapy.

Toxicity

A potential lethal dose for adults (without tolerance development) is usually in the range of 40-60 mg orally (30 mg parenterally). Scopolamine, hypnotics and alcohol potentiate toxic effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, ATC code: N02AA01

Morphine is an opioid analgesic with potent analgesic effect. The analgesic effect is partly due to an altered pain perception and partly on a raised pain threshold. Morphine probably exerts its analgesic effect at different levels within the CNS. In elderly patients the pain relieving effect of morphine increases. The central nervous system effects of morphine also include respiratory depression, psychiatric symptoms, nausea and vomiting, miosis and antidiuretic hormone release. The respiratory depressant effect of morphine is caused by the inhibition of the carbon dioxide stimulating effect on the respiratory centre in the medulla oblongata. This effect can lead to respiratory insufficiency in patients with impaired ventilation ability caused by pulmonary disease or other pharmaceuticals. Elderly may be more sensitive to the side effects. Intoxication with morphine requires respiratory supporting treatment and administration of antidote.
Morphine is metabolised via conjugation to the two main metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). Small amounts of morphine-3,6-diglucuronide can also be formed. M3G has a small affinity to opioid receptors, i.e. no documented analgesic effect, but can contribute to excitatory effects. M6G is twice as potent as morphine when systemically administered, and the pharmacologic effects of M6G cannot be separated from those of morphine. During chronic treatment it contributes with a significant part of the analgesic effects of morphine.

As a result of stimulation of dopamine receptors in the “trigger zone” in medulla oblongata, nausea and vomiting can occur. The increased release of antidiuretic hormone contributes to decreased urine volumes during morphine treatment. Morphine increases tonus in smooth muscles in the gastrointestinal tract. This causes obstipation due to a slower passage of food through the gastrointestinal tract. Further the pressure in the biliary passage and the urinary tract increases which makes morphine less suitable in biliary passage or urinary tract spasms.

Morphine has addictive properties and tolerance can develop against the morphine effects. However, normally this causes no problem in treatment of severe pain related to cancer.

5.2 Pharmacokinetic properties

The pharmacokinetics of morphine is not dose dependent.

Absorption
Maximum blood concentration is reached within 10-20 minutes.

Distribution
The volume of distribution of morphine is approximately 3 L/kg with a plasma protein binding of about 35 %. Morphine is widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen: lower concentrations appear in the brain and the muscles. Morphine crosses the placenta and is excreted into the breast milk (see section 4.6).

Biotransformation
Morphine is metabolised in the liver to the two main metabolites morphine-3-glucuronide (lacks analgesic effect but can contribute with excitatory effects) and morphine-6-glucuronide (M6G) (more potent than morphine itself). Small amounts of morphine-3,6-diglucuronide can also be formed. Morphine and its metabolites undergo enterohepatic circulation.

Elimination
Morphine is primarily eliminated via glucuronidation, and the excretion of unchanged morphine in the urine is 5-10 %. Clearance is approximately 24 mL/min*kg and the half-life is about 2-3 hours. Up to 10 % of a dose may be excreted via the bile into the faeces. M6G is excreted via urine, which causes M6G accumulation in renal impairment.

Special population
The morphine bioavailability can increase in liver cancer patients.

Hepatic impairment
Impaired hepatic function influence the elimination of morphine.

Renal impairment

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. There have been no long-term animal studies on the
tumorigenic potential of morphine. Effects in non-clinical studies were observed for genotoxicity, and toxicity to reproduction and development.

**Mutagenic and tumorigenic potential**
There are clearly positive findings available with regards to mutagenicity, which indicate that morphine has a clastogenic effect and that, furthermore, this effect exerts an influence on gametes. Thus, morphine is to be regarded as a mutagenic substance and such an effect may also be assumed in humans.

**Reproductive toxicity**
Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (CNS malformations, growth retardation, testicular atrophy, changes in neurotransmitter systems and behavioural patterns, dependence). In addition, morphine had an effect on male sexual behaviour and fertility in various animal species. In male rats, reduced fertility and chromosomal damage in gametes have been reported.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Hydrochloric acid (for pH adjustment)
Water for injections

6.2 **Incompatibilities**

Morphine salts are sensitive to pH changes and can precipitate in alkaline environment. Compounds incompatible with morphine salts include aminophylline, sodium salts of barbiturates, phenytoin and ranitidine hydrochloride. Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5-fluorouracil.

6.3 **Shelf life**

3 years.

6.4 **Special precautions for storage**

Store in the original package in order to protect from light.

6.5 **Nature and contents of container**

Colourless glass ampoules 10 x 1 ml.
5 ampoules are packed in a polyethylene film liner. 2 liners are packed in a carton.

6.6 **Special precautions for disposal and other handling**

Splashes on the skin and in the eyes can cause burning pain, redness and pruritus. Avoid direct contact with the product.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. **MARKETING AUTHORISATION HOLDER**
8. MARKETING AUTHORISATION NUMBER(S)
[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT
2018-12-19